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EXAMINER	
ASHEN, JON BENJAMIN	

ART UNIT	PAPER NUMBER
1635	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/089,525	MARTH ET AL.	
	Examiner	Art Unit	
	Jon B. Ashen	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11/24/2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-28* is/are pending in the application.

4a) Of the above claim(s) *13-28* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group II, claims 1-12 in the reply filed on 11/24/2004 is acknowledged. The traversal is on the ground(s) that Group I and Group II share a special technical feature according to PCT rule 13.2 and that in light of this, restriction between Group I and II should be withdrawn. This argument is found persuasive and Groups I and II have been rejoined for the purposes of examination in this application. It is noted herein that no other supposed errors in the restriction requirement between Groups I and II and any other of Groups III-VIII, as set forth in the restriction requirement, were distinctly and specifically pointed out by Applicant.

The requirement is still deemed proper and is therefore made FINAL.

Status of Application

2. Claims 1-28 are pending in the instant application. Claims 13-28 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 11/24/2004. Claims 1-12 are currently under examination in this application.

Information Disclosure Statement

3. The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Double Patenting

4. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

5. Claims 1- 5 and 8-12 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 2, 5 and 8-10 of U.S. Patent No. 6,376,475 in view of Tsuji 1996 (J. Biochem. Vol. 1, pp. 1-14). Although the conflicting claims are not identical, they are not patentably distinct from each other for the following reasons. The scope of claims 1, 2, 5

and 8-10 of U.S. Patent No. 6,376,475 is broadly drawn such that it either fully encompasses, or overlaps in claimed subject matter, with claims 1-5 and 8-12 of the instant application. U.S. Patent No. 6,376,475 and the instant application both encompass a method of administering an agent, to a mammal wherein the agent inhibits the activity of a sialyltransferase involved in the biosynthesis of a Siaα2,3Galβ1-3GalNAc moiety and wherein the agent can be any agent. The instant claims are drawn to a species of agent that increases or decreases the activity of ST3Gal-IV sialyltransferase wherein the agent can be any agent including an antisense nucleic acid. Claims 1, 2, 5 and 8-10 of U.S. Patent No. 6,376,475 are drawn to a genus of agents that inhibit the activity of any sialyltransferase involved in the biosynthesis of a Siaα2,3Galβ1-3GalNAc moiety. Tsuji teaches that, the substrate preference of ST3Gal-IV sialyltransferase cloned from human placenta is for Galβ1-3GalNAc, which would yield a sialylated Siaα2,3Galβ1-3GalNAc moiety (pg. 5). Therefore, an invention that is a method of administering an agent that inhibits the activity of a sialyltransferase involved in the biosynthesis of a Siaα2,3Galβ1-3GalNAc moiety would make obvious a method of administering an agent that would cause a decrease in ST3Gal-IV sialyltransferase activity because a method of inhibiting the activity of any sialyltransferase involved in the biosynthesis of a Siaα2,3Galβ1-3GalNAc moiety was known in the art and because Tsuji teaches a particular sialyltransferase involved in the above biosynthesis.

6. Claims 1-5 and 8-12 of the instant application are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3, 6-9 and 41-43 of copending Application No. 10/131,721. Although the conflicting claims are not identical, they are not patentably distinct from each other for the following reasons. The scope of claims 1-5 and 8-12 of the instant application is broadly drawn such that it either fully encompasses, or overlaps in claimed subject matter, with claims 1-3, 6-9 and 41-43 of copending Application No. 10/131,721. Copending Application No. 10/131,721 and the instant application are both drawn to a method of administering an agent that reduces the amounts of a cell-surface sialylated oligosaccharide wherein the sialylated oligosaccharide comprises a terminal α2-3-linked sialic acid, wherein the agent can be an inhibitory nucleic acid that inhibits expression of a gene encoding a glycosyltransferase (which would include both ST3Gal I and ST3Gal IV sialyltransferases) involved in the synthesis of the sialylated oligosaccharide.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

7. Instant claims 1-5 and 8-12 are directed to an invention not patentably distinct from that of claims 1-3, 6-9 and 41-43 of commonly assigned, copending Application No. 10/131,721 (see section 6 above).

The U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common

ownership (see MPEP § 2302). Commonly assigned copending Application No. 10/131,721 discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(e), (f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee can, under 35 U.S.C. 103(c) and 37 CFR 1.78(c), either show that the conflicting inventions were commonly owned at the time the invention in this application was made, or name the prior inventor of the conflicting subject matter.

A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications filed on or after November 29, 1999.

8. Claims 1-5 and 8-12 of the instant application are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-11, 16-20 and 25 of copending Application No. 10/398,520. Although the conflicting claims are not identical, they are not patentably distinct from each other for the following reasons. The scope of claims 1-5 and 8-12 of the instant application is broadly drawn such that it either fully encompasses, or overlaps in claimed subject matter, with claims 1-11, 16-20 and 25 of copending Application No. 10/398,520. Copending Application No.

10/398,520 and the instant application are both drawn to a method of administering an agent that reduces the amounts of a cell-surface sialylated oligosaccharide wherein the sialylated oligosaccharide comprises a terminal α2-3-linked sialic acid, wherein the agent can be an antisense nucleic acid that inhibits expression of a gene encoding a glycosyltransferase (such as ST3Gal IV sialyltransferase which is an alpha 2,3 sialyltransferase) involved in the synthesis of the sialylated oligosaccharide. Claims in both the instant and copending applications which require co-administration (either in conjunction with or prior to) with a drug for which blood clotting or inflammation is a potential side effect are obvious over each other because both conditions are a result of reducing the level of biosynthesis of alpha 2,3 sialic acid terminated oligosaccharides.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 1-12 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the

time the application was filed, had possession of the claimed invention. This is a written description rejection.

Claims 1-12 are drawn to a method for modulating levels of vWF or FVIII in an animal by administering an agent that causes an increase or a decrease in ST3Gal-IV sialyltransferase activity in the animal (claim 1) wherein the method decreases levels of vWF or FVIII and the agent decreases ST3Gal-IV activity (claim 2) wherein the agent decreases expression of a gene that encodes ST3Gal-IV (claim 3), wherein the agent is an antisense nucleic acid that hybridizes to an ST3Gal-IV encoding nucleic acid (claim 4), wherein the agent inhibits enzymatic activity of an ST3Gal-IV polypeptide (claim 5) wherein the method is performed in conjunction with administration of a drug for which blood clotting is a potential side effect (claim 6) wherein the agent is administered before or simultaneously with said drug (claim 7) wherein the method is performed as a prophylactic or therapeutic measure against atherosclerosis (claims 8 and 10 respectively) wherein the atherosclerosis is associated with coronary artery disease or peripheral vascular disease (claims 9 and 11 respectively) wherein platelet formation is not significantly affected by administration of the agent to the animal (claim 12).

Claims 1-3 and 5-12 read broadly on a method of treatment that functions in any animal by administering any agent that causes any increase or any decrease in any ST3Gal-IV sialyltransferase activity in the animal. Claim 4 broadly on a method of treatment that functions in any animal by administering

any antisense nucleic acid that causes any increase or any decrease in any ST3Gal-IV sialyltransferase activity in the animal.

The specification provides no definition what is encompassed by the agent or the antisense nucleic acid of the invention as claimed and no guidance as to what agent or antisense nucleic acid, that can be any agent or any antisense nucleic acid, will function in the method as claimed. The specification discloses examples of a single mammal that appears to be related to their invention as claimed that are heterozygous and null knockout mice in which the ST3Gal-IV sialyltransferase gene has been disrupted. However, the specification does not disclose any agent or any antisense nucleic acids that are used to treat these animals.

The specification provides only limited and general guidance in regards sialyltransferase inhibitors that are known in the art to function in vitro and indicates that ST3Gal-IV activity can be regulated by modulation of the phosphorylation state of the enzyme, also in vitro (pg. 13). The specification further discloses that, "Additional inhibitors of the ST3Gal-IV sialyltransferase can be readily identified by screening methods known to those of skill in the art" and that these methods are assays of enzyme activity that are carried out in vitro (pg. 14). The specification provides only limited guidance in regards to inhibitory or antisense nucleic acids and how they may be used in general, that the nucleotide sequence of human ST3Gal-IV is known in the art, that this sequence can be used as a probe to identify other ST3Gal-IV encoding nucleic acids from other

species and that from "human or other ST3Gal-IV encoding nucleotide sequences, one can derive suitable inhibitory nucleic acids" (pgs. 16-17).

The specification, however, provides no examples of agents or antisense nucleic acids that function *in vivo*, to provide the method of treatment as claimed. Additionally, the specification provides no specific guidance that would lead one skilled in the art to the structure of a specific molecule that would function as an agent or antisense nucleic acid in the method of treatment as claimed.

The specification provides no structure of an agent that can be any agent or of an antisense nucleic acid that can be any antisense nucleic acid that would correspond with the function of providing a treatment by practicing the method as claimed. Additionally, the specification provides no evidence for any shared distinguishing identifying characteristics of an agent or of an antisense nucleic acid that would be a shared and defining characteristic for either genus as claimed. No structure is provided of any species of agent or antisense nucleic acid disclosed within the scope of the claimed genera that corresponds with the function providing a treatment as claimed. To provide evidence of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof.

In the instant case, what is the structure of an agent that can be any agent or of an antisense nucleic acid that can be any antisense nucleic acid that would

function to cause any increase or any decrease in any ST3Gal-IV activity in any animal such that a treatment was provided, for example?

Applicant, therefore, has claimed a method of achieving a biological effect but has disclosed no compounds that can accomplish that result. Applicant has only provided an invitation for further experimentation to determine what particular agents or antisense nucleic acids could be used in the method of treatment as claimed. Applicant has not provided an adequate written description that indicates that applicant was in possession of a method of treatment because said method of treatment relies on the function of an agent for which a structure that corresponds with said function is not adequately described; i.e., any agent or any antisense nucleic acid that would function to cause any increase or any decrease in any ST3Gal-IV activity in any animal such that a treatment was provided

Vas-Cath Inc. v. Mahurkar, 19USPQ2nd 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the "written description" inquiry, whatever is now claimed (see page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed." (see *Vas-Cath*, pg 1116). In the instant case, a person of ordinary skill in the art cannot envision an exact structure for any inhibitory or antisense nucleic acid agent to be used in a method of treatment that would effect the multiple genera of biological responses, entities or quantities as claimed and outlined above.

Adequate written description for the invention as claimed requires more than statements that disclose a single or several species of the invention when the claims are drawn to the entire genus. In particular, in the instant case, no species of the invention are disclosed as agents or antisense nucleic acids that function in the method of treatment as claimed.

The claimed method depends on finding an agent or an antisense nucleic acid that will function in the method of treatment as claimed. Without such an agent or antisense nucleic acid, it is impossible to practice the method as claimed. It means little to invent a method if one does not have possession of an agent or antisense nucleic acid that is essential to practicing that method. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. § 112 is severable from its enablement provision (see pg 1115).

Therefore, applicant has not provided an adequate written description of the invention.

11. Claims 1-12 are also rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. In the instant case, the specification does not provide an adequate written description of the agent or antisense nucleic acid of the invention that is required to practice the method of

the invention as now claimed (see previous rejection herein). Therefore, because the skilled artisan cannot envision any particular agent or antisense nucleic acid of the invention that will function in the method of treatment or prevention as claimed, the specification does not enable a person skilled in the art to which it pertains to make and use the invention as claimed.

The following factors as enumerated *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), are considered when making a determination that a disclosure is not enabling: the breadth of the claims, the nature of the invention, the state of the prior art, the level of ordinary skill in the art, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples and the quantity of experimentation needed to make the invention based on the content of the disclosure.

Claims 1-12 are drawn to a method for modulating levels of vWF or FVIII in an animal by administering an agent that causes an increase or a decrease in ST3Gal-IV sialyltransferase activity in the animal, the full breadth of which is described in a previous rejection herein. All claims read broadly on a method of treatment comprising administering any agent or any antisense nucleic acid. In particular, claims 8 and 9 are drawn to a prophylactic method.

The specification, however, does not support the broad scope of the claims which encompass a method for modulating any levels of vWF or FVIII in any animal by administering any agent or any antisense nucleic acid that causes any increase or any decrease in any ST3Gal-IV sialyltransferase activity in the animal. Additionally, the specification as filed provides no support for claims to

an agent that will act as a prophylactic of atherosclerosis, in any animal, wherein that agent can be any agent that causes an increase or decrease in ST3Gal-IV sialyltransferase activity. Prophylactic, as defined by Webster's II New Riverside University Dictionary, means, "Serving to defend against or prevent something, esp. disease: PROTECTIVE" (pg. 944; also see the definition of prevent, pg. 933). Applying the dictionary definition to prophylactic, a reasonable interpretation of the nature of the invention is a method of preventing atherosclerosis due to any cause by administering any agent that causes an increase or decrease in any ST3Gal-IV sialyltransferase activity in any animal. The specification does not establish a predictable scheme for treating or preventing atherosclerosis by reducing or increasing the activity of ST3Gal-IV in any animal using any agent, or for any antisense nucleic acid that inhibits the gene expression of any ST3Gal-IV sialyltransferase with an expectation of obtaining the desired biological function. The specification provides no specific guidance and presents no specific disclosures that would allow the skilled artisan to envision what agents or antisense nucleic acid would be required to practice a method of prevention or treatment as claimed.

The disclosures of the specification provide information concerning the biological effects of disrupting ST3Gal-IV sialyltransferase activity in knockout heterozygous and null mice. This disclosure provides a starting point for a series of experiments that would be required to determine how to formulate a method of prevention or treatment as claimed, including a full characterization of the functional regions of all other ST3Gal-IV gene sequences and the determination

of the particular effects of modulating ST3Gal-IV gene expression or ST3Gal-IV sialyltransferase activity on the levels of vWF and/or FVIII in all other animals. Once determined, the information from the above experiments could be used in a further series of experiments to determine what particular agents or antisense nucleic acids would be required to provide a prevention or treatment as claimed. Therefore, applicant has only provided an invitation for further experimentation, since the specification is entirely prophetic in regards to a method of prevention or treatment as claimed, and provides no specific guidance for determining how the skilled artisan would practice the method of prevention or treatment of the instant invention.

Additionally, because the breadth of the claims is so broad and because no specific or functional species of agent or antisense nucleic acids that would be necessary to practice the method of prevention or treatment as claimed are disclosed in the specification, the skilled artisan would have to perform an extremely large and undue quantity of de novo trial and error experimentation (as indicated above) in order to determine, *de novo,* the structure and function of an agent or antisense nucleic acid that would function to cause an increase or decrease in ST3Gal-IV sialyltransferase activity so as to provide an in vivo prevention or treatment as claimed.

The state of the prior art at the time of filing recognizes a broad genus of agents and antisense nucleic acids that can have biological effects in animals, including the effect of inhibiting enzyme activity or gene expression. Such agents can include small molecules, peptides, aptamers, antibodies,

siRNAs, ribozymes and sense and antisense oligonucleotides, for example. However, sound scientific reasoning requires that although such agents can have the effects set forth above, determination of a particular and desired biological effect that results from a method of treatment using a specific agent, would require, at least, that agent. Without the agent such a determination cannot be made.

In particular, with regard to antisense nucleic acids, the state of the art at the time of filing relative to the enablement of nucleic acid therapies *in vivo* is reviewed by Opalinska et al. 2002 (Nature Reviews, Vol. 1, pp. 503-514). These authors provide a review of the challenges that remain before nucleic acid therapy becomes routine in therapeutic settings and clearly indicate that the art of nucleic acid therapy remains highly unpredictable and unreliable, particularly *in vivo*. According to Opalinska et al., "Although conceptually elegant, the prospect of using nucleic acid molecules for treating human malignancies and other diseases remains tantalizing, but uncertain. The main cause of this uncertainty is the apparent randomness with which these materials modulate the expression of their intended targets. It is a widely held view that molecule delivery, and selection of which messenger RNA sequence to physically target, are core stumbling blocks that hold up progress in the field" (pg 503). Opalinska et al. also note that .. "[I]t is widely appreciated that the ability of nucleic acid molecules to modify gene expression in vivo is quite variable and therefore wanting in terms of reliability. Several issues have been implicated as a root cause of this problem, including molecule delivery to targeted cells and specific compartments

within cells, and identification of sequence that is accessible to hybridization in the genomic DNA or RNA" and "In mRNA, sequence accessibility is dictated by internal base pairing and the proteins that associate with the RNA in a living cell. Attempts to accurately predict the in vivo structure of RNA have been fraught with difficulty. Accordingly, mRNA targeting is largely a random process" (pg. 511). The instant specification does not show how one in the art might overcome the obstacles to providing antisense therapy as outlined above or how applicant has overcome the same general obstacles to antisense therapy in the instant invention.

This view is supported by Branch (1998) who teaches that "Scientist seek to use the [antisense] molecules to ablate selected genes and thereby understand their functions and pharmaceutical developers are working to find nucleic acid based therapies. However, the antisense field has been turned on its head by the discovery of 'non-antisense' effects, which occur when a nucleic acid drug acts on some molecule other than its intended target-often through an entirely unexpected mechanism." In addition, Branch also teaches that the successful delivery of antisense/ribozymes *in vivo* is unpredictable wherein they recite, "Recent studies emphasize the extent to which native RNA structure restricts the binding of ODN's... [B]ecause it is very difficult to predict what portions of an RNA molecule will be accessible *in vivo*, effective antisense molecules must be found empirically by screening a large number of candidates for their ability to act inside cells. Monia and co-workers used northern hybridization to screen 34 20-nt long s-ODNs complementary to c-*raf* kinase and

found only one that yielded a greater than fivefold reduction in the target mRNA. Thus only 3% of the antisense molecules tested in this system were highly effective, 40% had almost no effect." (pg. 49).

The state of the prior art at the time of filing recognizes that there is a high degree of unpredictability in the art of *in vivo* nucleic acid therapy. There is no way of predicting, *a priori*, the ability to provide an *in vivo* treatment that relies on the modulation of gene expression or the efficacy of a treatment that relies on modulating gene expression comprising administering an agent that is any antisense nucleic acid.

Therefore, based on the nature of the invention as an in vivo method of prevention or treatment, the degree of unpredictability in the art of antisense nucleic acid therapy, the breadth of the claimed method as an *in vivo* method of prevention or treatment, the lack of guidance as to what particular species of agent or antisense nucleic acids would be required to practice the method as claimed, the need to screen multiple species of said agents or nucleic acids so as to allow identification of particular species as functional within the method as claimed and the quantity of *de novo* experimentation necessary to discover the above, an undue amount of experimentation would be required in order to practice the method of prevention or treatment as claimed. Therefore, the inventors have not enabled one skilled in the art perform the method of the claimed invention.

Claim Rejections - 35 USC § 102

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

13. Claims 1-5 and 8-12 are rejected under 35 U.S.C. 102(e) as being anticipated by Kapitonov et al. (U.S. Patent 6,280,989). The invention as set forth in claims 1-5 and 8-12 is outlined in a previous rejection herein (see section 10).

Kapitonov et al. disclose the identification of three novel classes of sialyltransferases, one of which is 4ST3Gal-IV (col. 2, lines 27-31). Kapitonov et al. also disclose that their invention relates to "methods of regulating a biological response in which a sialyltransferase or a homolog or modification thereof, of the present invention, participates, e.g., by modifying a substrate such as a glycoprotein or glycolipid which is a participant which leads to the ultimate cellular response. These pathways can be modulated by administering various agents including antibodies to sialyltransferases, polypeptide mimics of sialyltransferases (e.g., which compete for substrates of the enzyme, antisense

oligonucleotides, antisense mRNA, etc" (col. 16, lines 80-19) and that antisense oligonucleotides of the invention can be designed to specific regions of a sialyltransferase RNA and can then be administered to cells expressing such genes so as to inhibit expression (col. 18, lines 26-40) and that administering can mean contacting a cell or host in an effective manner with an agent of interest whereby the agent can modulate the activity of interest (col. 19, lines 65-67 bridge to col. 20, lines 1-2). It is noted herein, that claim limitations which require a reduction of ST3Gal-IV activity are met by an antisense nucleic acid that will inhibit the expression of ST3Gal-IV because this antisense nucleic acid acts to decrease the activity of ST3Gal-IV in an animal and to inhibit the enzymatic activity of a ST3Gal-IV polypeptide in that it reduces the overall levels of ST3Gal-IV. The disclosure of Kapitonov et al. is considered to be enabling for the methods disclosed to at least the same extent as the disclosure of the instant application is enabling for the instantly claimed methods

In particular regards to claims 8-12, a recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. In a claim drawn to a process of making, the intended use must result in a manipulative difference as compared to the prior art. See *In re Casey*, 152 USPQ 235 (CCPA 1967) and *In re Otto*, 136 USPQ 458, 459 (CCPA 1963). In the instant case, a method of administering an agent which causes an increase or a decrease in the activity of any

sialyltransferase involved in ST3Gal-IV activity in an animal would also be a method that is performed as a prophylactic or therapeutic against atherosclerosis or wherein platelet formation is not significantly affected by administration. This is particularly evident when considering that the disclosure of the specification does not set forth any method steps by which the method of administration now claimed is to be performed. Therefore, the prior art is applied on the basis of the prior art disclosure of the claimed composition. MPEP § 2111.02.

Therefore, Kapitonov et al. anticipate each and every aspect of the invention as set forth in claims 1-5 and 8-12.

Claim Rejections - 35 USC § 103

14. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

15. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of

35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

16. Claims 1-5 and 8-12 are rejected under 35 U.S.C. 103(a) as being obvious over Marth et al. (U.S. Patent No. 6,376,475) in view of Tsuji 1996 (J. Biochem. Vol. 1, pp. 1-14).

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). For applications filed on or after November 29, 1999, this rejection might also be overcome by showing that the subject matter of the reference and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person. See MPEP § 706.02(l)(1) and § 706.02(l)(2).The invention of

the instant application as set forth in claims 1-5 and 8-12 is outlined in a previous rejection herein.

Marth et al. disclose and claim a method for inhibiting an immune response mediated by lymphocytes in a mammal comprising administering an agent that inhibits the activity of a sialyltransferase involved in the biosynthesis of a Siaα2,3Galβ1-3GalNAc moiety thereby inhibiting a T lymphocyte-mediated response in the mammal (col. 2, "Summary of the Invention" and claim 1). Marth et al. disclose nucleic acid agents that inhibit sialyltransferase gene expression and that the agent of their invention can be an inhibitory nucleic acid wherein they state that, "Other embodiments of the invention involve administrating an inhibitory nucleic acid that specifically hybridizes to a target nucleic acid that encodes an ST3Gal sialyltransferase..." (col. 16).

Marth et al. do not teach a method of modulating levels of vWF and/or FVIII by administering an agent that causes specific inhibition of ST3Gal-IV sialyltransferase. However, a recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. In a claim drawn to a process of making, the intended use must result in a manipulative difference as compared to the prior art. See *In re Casey*, 152 USPQ 235 (CCPA 1967) and *In re Otto*, 136 USPQ 458, 459 (CCPA 1963). In the instant case, a method of administering an agent which caused a decrease in the activity of any sialyltransferase involved in the biosynthesis of a

Siaα2,3Galβ1-3GalNAc moiety in a mammal would also be a method of administering an agent that caused a decrease in ST3Gal-IV sialyltransferase in an animal. This is particularly evident when considering that the disclosure of the specification does not set forth any method steps by which the method of administration now claimed is to be performed. Therefore, the prior art is applied on the basis of the prior art disclosure of the claimed composition. MPEP § 2111.02.

Tsuji teaches that, the substrate preference of ST3Gal-IV sialyltransferase cloned from human placenta is for GalB1-3GalNAc, which would yield a sialylated Siaα2,3Galβ1-3GalNAc moiety (pg. 5).

It would have been obvious to one of ordinary skill in the art to practice a method for modulating levels of vWF or FVIII in an animal comprising administering an agent to the animal that causes a decrease in the activity of a ST3Gal-IV sialyltransferase in the animal because Marth et al. disclose and claim a method of inhibiting the activity of any sialyltransferase involved in the biosynthesis of a Siaα2,3Galβ1-3GalNAc moiety and because Tsuji teaches that ST3Gal-IV is involved in the biosynthesis of a Siaα2,3Galβ1-3GalNAc moiety.

One of ordinary skill in the art would have been motivated to practice such a method because, as disclosed by Marth et al., ST3Gal sialyltransferases are involved in modulating the T lymphocyte-mediated immune response in mammals by inhibiting the activity of any sialyltransferase involved in the biosynthesis of a Siaα2,3Galβ1-3GalNAc moiety and because ST3Gal-IV was known to be involved in the biosynthesis of a Siaα2,3Galβ1-3GalNAc moiety.

One of ordinary skill in the art would have expected success in practicing such a method because a method of inhibiting an immune response in a mammal by administering an agent that caused a decrease in the activity of a ST3Gal sialyltransferase involved in the biosynthesis of a Siaα2,3Galβ1-3GalNAc moiety was already successful in the art and because ST3Gal-IV was known to be involved in the biosynthesis of a Siaα2,3Galβ1-3GalNAc moiety.

Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

17. No claims currently under examination in this application are in condition for allowance. Claims 6-7 are free of the prior art searched.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon B. Ashen whose telephone number is 571-272-2913. The examiner can normally be reached on 7:30 am - 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached on 571-272-0670. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public. For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Jba